INDEX NUMBER

Vol. 68, No. 12 Established 1891 December 1951

ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

LEADING ARTICLES IN THIS NUMBER

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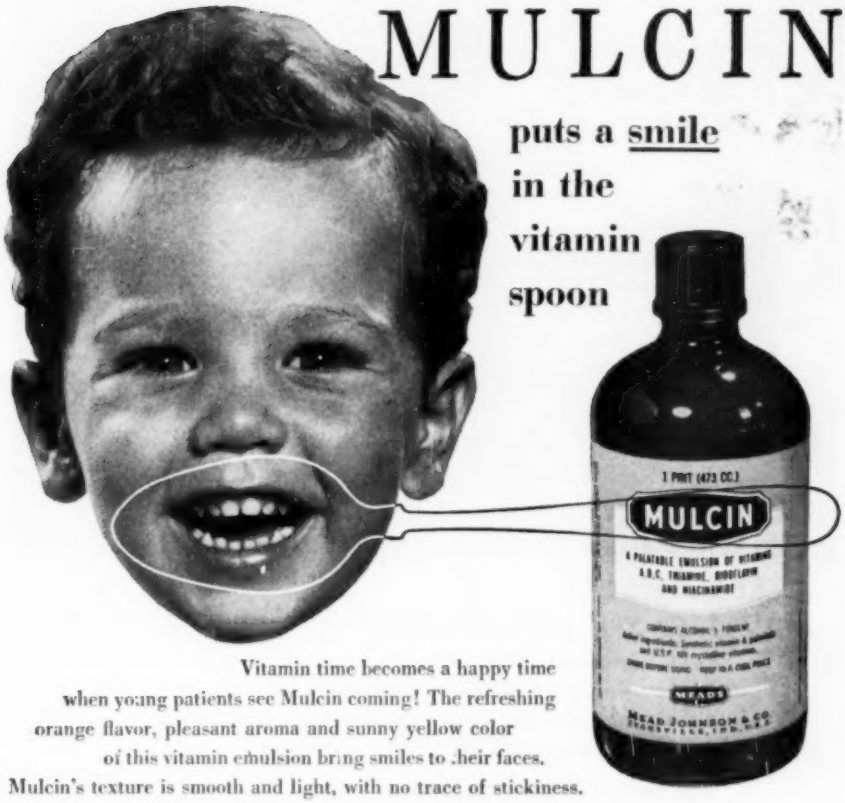

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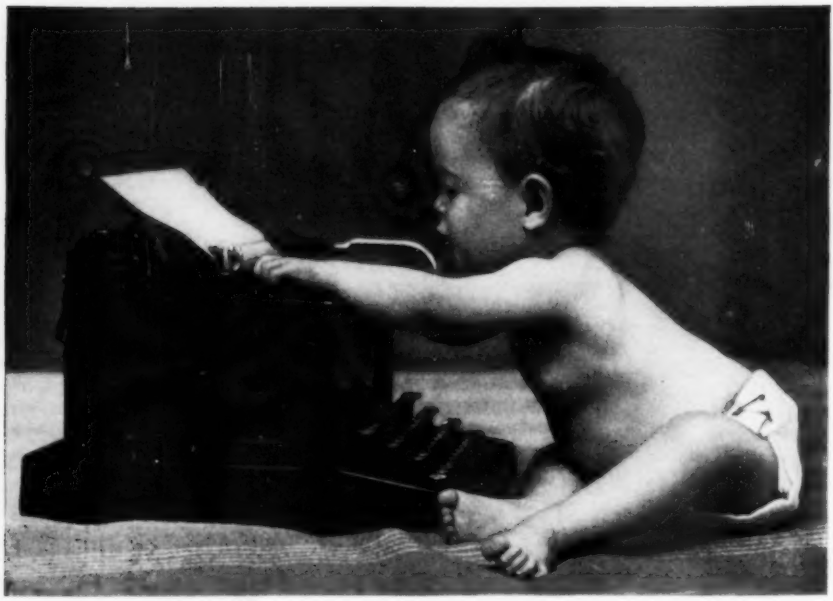

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ORIGINAL ARTICLES

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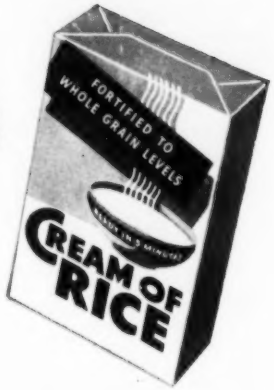

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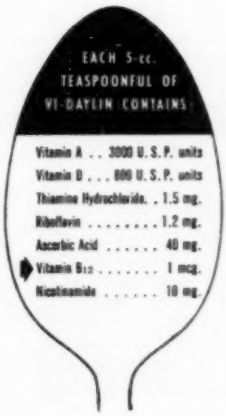

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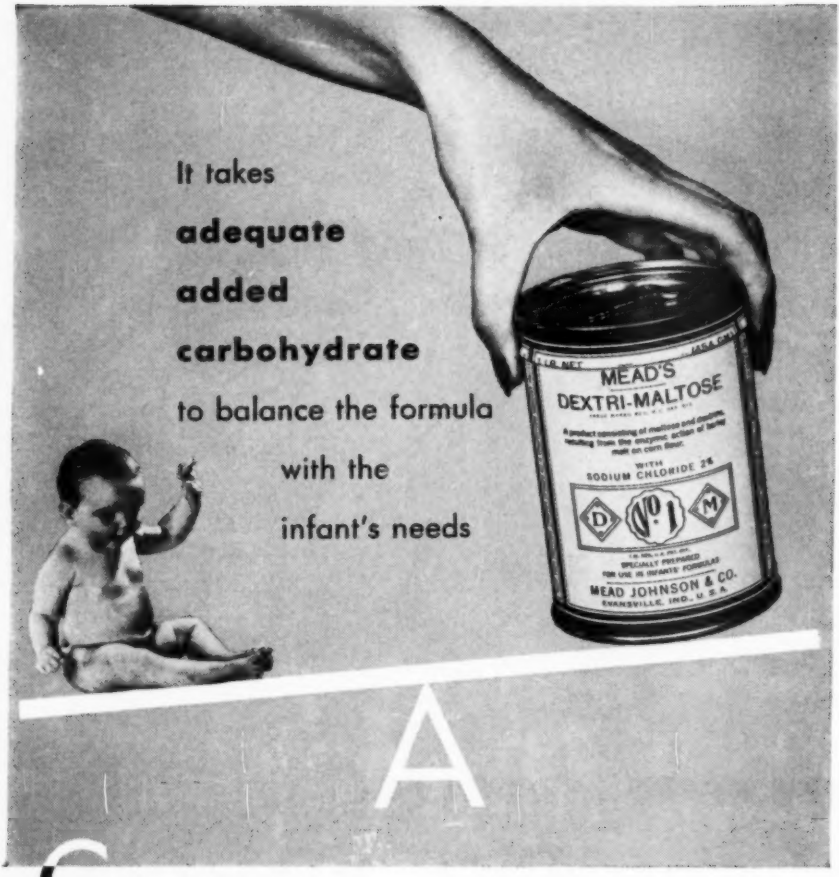

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CURVE B

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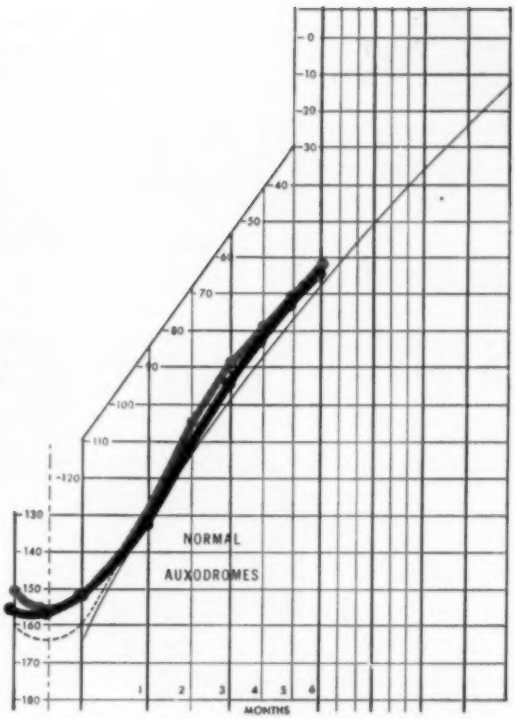

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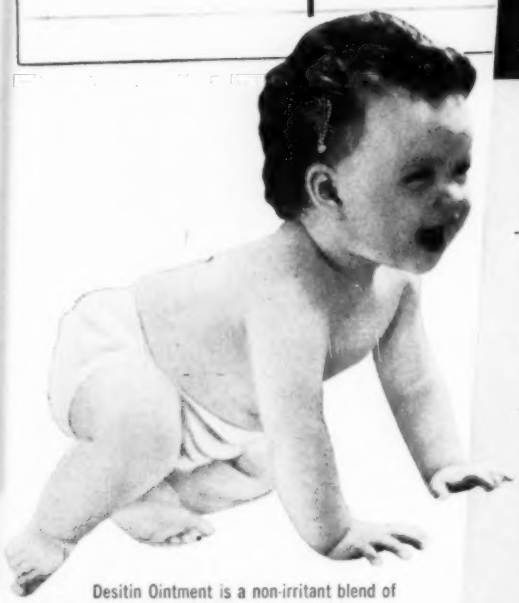

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ARCHIVES OF PEDIATRICS

VOL. 68 DECEMBER 1951 No. 12

JOHN FITCH LANDON, M.D., Editor

THE ROLE OF BLOOD INCOMPATIBILITY IN THE ETIOLOGY OF ICTERUS NEONATORUM*

GERALDINE WEIN, M.D.
New York.

The etiology of icterus neonatorum has been a controversial issue ever since this entity was first recognized. With our recent acquisition of knowledge concerning blood groups and the consequences of blood incompatibility, there has been considerable interest in the possible relationship between this factor and icterus neonatorum. The following study was an attempt to determine what role, if any, infant-mother blood incompatibility plays in the development of physiological jaundice.

METHOD AND MATERIALS

One hundred twenty-three consecutive mothers and newborns, selected from the obstetrical and newborn services of Metropolitan Hospital, New York City, were studied in regard to their blood A-B-O and Rh types. Blood Wassermanns were obtained on all mothers. The babies were all five pounds or over at birth, and were essentially healthy, normal newborns, delivered spontaneously or by low forceps. The presence of jaundice was determined by clinical observation. Quantitative serum bilirubin, icterus index, and van den Bergh reactions were obtained on all infants who developed jaundice during their hospital stay.

*Submitted as part of the requirements for the Post-graduate Course in Pediatrics, New York Medical College, Flower and Fifth Avenue Hospitals, New York City.

RESULTS

Twenty-two of the 123 infants studied developed clinical icterus during the first five days of life. All of these cases were investigated to rule out other causes for the icterus before it was concluded that they had physiological jaundice. Two of these 22 infants presented typical pictures of erythroblastosis fetalis, with high maternal antibody titers, positive Coombs' tests, hemolytic anemia with numerous erythroblasts in the peripheral smear, and hepatosplenomegaly. These cases have been excluded from the study. The overall incidence of icterus neonatorum was then 16.5 per cent.

If we consider just those infants who exhibited a potential Rh incompatibility with their mothers, we find an incidence of jaundice of 15.4 per cent.; 17.3 per cent of infants who had the same Rh type as their mothers developed icterus. (Table 1). However, the group of infants whose blood types showed an A-B-O incompatibility with their mothers had a 30.4 per cent incidence of jaundice (Table 2).

TABLE 1. *Incidence of Jaundice in Rh Compatible and Incompatible Infants*

Rh		Number of Cases	Number of Jaundiced Cases	% of Cases Jaundiced
Infant	Mother			
+	+	102	17	16.7%
+	—	13	2	15.4%
—	+	4	0	0
—	—	2	1	50%

The laboratory determinations of the icterus index and serum bilirubin levels confirmed our diagnosis of jaundice in every case. However, there was no significant difference in the levels of these factors in the compatible and incompatible groups.

DISCUSSION AND CONCLUSIONS

The overall incidence of icterus neonatorum observed in this series (16.5 per cent) was considerably lower than the range

reported by other investigators.[1-3] It is possible that some cases were missed, since clinical evaluation of jaundice is often difficult, particularly in the artificial light of the nursery. It is also conceivable that some cases of icterus may have developed after dis-

TABLE 2. *Incidence of Jaundice in A-B-O Incompatible Infants*

A-B-O Group Infant	Mother	Number of Cases	Number of Jaundiced Cases	% of Cases Jaundiced
A or B	O	23	7	30.4%
A	B	11	2	18.2%
B	A			
AB	A or B			

charge from the hospital. The newborn infants remain in this hospital for only four to six days, and it was not possible for us to observe these patients subsequent to discharge. Since icterus neonatorum is usually described as appearing on the second to fourth day of life,[4] either our incidence was below average for some undetermined reason, or else there was an appreciable number of infants who manifested jaundice later than the usually quoted time.

TABLE 3. *Comparison of Incidence of Jaundice in Various Groups Studied*

Group	% Jaundiced
Total Group of Infants Studied	16.5%
Infants With Rh Incompatibility	15.4%
Infants With Rh Compatibility	17.3%
Infants With A-B-O Incompatibility	30.4%

Our results indicate that there is essentially no difference in the incidence of icterus neonatorum among Rh compatible, clinically inactive Rh incompatible infants, and the group as a whole (Table 3). Moreover, infants exhibiting a potential A-B incompatibility with their mothers did not develop a significantly higher incidence of jaundice of the newborn. On the other hand, in

contrast to the recent findings of Wexler and Wiener,[5] the incidence of jaundice in the A-B-O incompatible infants was almost twice that seen in the other groups. These findings tend to substantiate the conclusions of Rondinini and Fortunato.[6]

Interestingly enough, none of these infants with A-B-O incompatibility developed their icterus within the first twenty-four hours of life, and so would not fall into the icterus precox group described by Halbrecht,[7,8] unless we extend the period during which this entity occurs to forty-eight hours.

Although this series of cases is too small to warrant any definite conclusions, it would appear that an A-B-O incompatibility may be the factor in some cases of so-called physiological jaundice.

SUMMARY

1. One hundred twenty-three pairs of mothers and newborn infants were studied in regard to their blood A-B-O and Rh types, and the relationship between these factors and the development of icterus neonatorum was determined.

2. The incidence of icterus neonatorum in this series was 16.5 per cent, indicating that either an appreciable number of infants developed jaundice later than the first five days of life, or that there was a decreased incidence of physiological jaundice from that usually quoted in the literature.

3. The incidence of icterus neonatorum does not appear to be affected by the Rh compatibility or incompatibility of mother and child.

4. There may be a relationship between some cases of so-called icterus neonatorum and the presence of an A-B-O incompatibility between mother and infant.

Acknowledgements. The author wishes to express her gratitude to Dr. Joseph Schwartzman for his invaluable aid and advice, and to Dr. Irwin Schiff for having stimulated interest in this problem.

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CAUSE OF RHEUMATIC FEVER—CHRONIC SINUSITIS

EDWARD E. BROWN, M.D., F.A.A.P.
Ashland, Ore.

Before the cause of rheumatic fever can be considered established, six pertinent observations must be explained and correlated. They are: (1) high incidence of preceding upper respiratory infections; (2) increased antistreptolysin titers prior to, and at the onset of, the disease; (3) failure of tonsillectomy to prevent recurrences of rheumatic fever; (4) variety of organisms cultured in rheumatic fever; (5) geographical variations and (6) seasonal variations in incidence.

In the following article these six observations are correlated to show first, that the etiologic agent is the hemolytic streptococcus, and second, that the focus is chronic sinusitis.

1. *High Incidence of Upper Respiratory Infection Preceding Rheumatic Fever.* The reported incidence of preceding infection varies from 70 to 95 per cent.[1-5] McCulloch and Irvine-Jones,[4] in a study of 204 attacks of rheumatic disease, stated that only 28 did not follow an obvious upper respiratory infection. This prior respiratory infection is often overlooked unless specific inquiry is made regarding it.[6] Rosenberg,[5] in a series of 1,000 patients studied at a large naval hospital, wrote that "in almost all our patients, there was a recent history of an acute upper respiratory infection, such as coryza, sinusitis, pharyngitis, tonsillitis or otitis media, which occurred one to four weeks prior to the onset of rheumatic fever."

I have elsewhere indicated that most "colds" are acute exacerbations of a chronic sinusitis caused by the hemolytic streptococcus and not by a virus.[7] A mass onset of colds takes place in chilling weather almost simultaneously throughout the country.[8-11] Such endogenous colds are accompanied by a dissociation of the ubiquitous alpha streptococcus to a beta streptococcus (see observation 4 below).

The alpha streptococcus is probably present in 100 per cent of infected sinuses and may be cultured from all pharynges.[12, 13] Various streptococci were found by Kistner in 94.5 per cent of infected sinuses.[14] The alpha streptococcus dissociates to the beta streptococcus when the patient's resistance is lowered by chilling, resulting

in the upper respiratory infection.[7] Sewall[15] states: "The hemolytic streptococcus located in the tissues, produces the active and complicated process known as the common cold." He finds beta streptococci deep in the mucous membranes of the sinuses, whereas weakened dissociants (alpha streptococci) are extruded in the purulent exudates.

2. *High Incidence of Elevated Antistreptolysin Titers which Precede and Accompany Rheumatic Fever.* An elevated antistreptolysin titer is commonly noted just before and at the onset of rheumatic fever and is strong presumptive evidence incriminating the hemolytic streptococcus.[16]

3. *Failure of Tonsillectomy to Prevent Recurrences of Rheumatic Fever.* That the sinuses are the etiologic focus for the causative organism is suggested by the following evidence which rules out tonsils, teeth and pharynx as foci.

Since tonsillectomy is performed in most rheumatic children without significant reduction in the number of recurrences of rheumatic fever,[17, 18], the focus harboring the hemolytic streptococcus must be sought elsewhere. In Wasson and my series of 100 children, 86 per cent were tonsillectomized.[19] The teeth of our rheumatic children were placed in good repair,[19] ruling out this potential focus. The only consistent focus was chronic sinusitis.

During a rheumatic episode the hemolytic streptococcus may be cultured from the pharynx, usually reaching this area from infected sinuses. The pharynx cannot act focally since it does not produce *pus under pressure*, a necessary attribute of a focus of infection.[20-23]

Because pus finds difficult egress through small sinal ostia, toxins are forced under pressure to the nearest lymph nodes, accounting for a high incidence of lymphadenitis, despite tonsillectomy, in *ambulant* rheumatic children, as follows: cervical, 88 per cent; submaxillary, 84 per cent; retropharyngeal, 22 per cent.[19] At the onset of an acute attack of rheumatic fever, and during an exacerbation, the incidence of lymph node involvement is even higher.

4. *Variety of Organisms Cultured in Rheumatic Fever.* Perhaps the main deterrent to the general acceptance of the hemolytic stretptococcus as the cause of rheumatic fever has been failure to recover this organism consistently from blood and joints. There are at least two reasons for this discrepancy. The first is the major

role of streptococcal *toxins,* rather than the streptococcus itself, in producing rheumatic pathology. The second is the ready dissociation of the hemolytic streptococcus.

Rosenow, Hadley, Mellon, Callow, d'Herelle, Hadjopoulos, Burbank and others familiar with streptococcic dissociation have shown the numerous variants which appear in blood and joints when defense mechanisms act on the hemolytic streptococcus. As Burbank[24] puts it, "the organism changes its nature from one with invasive properties to one more parasitic in character, thus avoiding the strong immunologic reactions of the host, which would kill it." At the onset of rheumatic fever, Cecil[25] recovered from the blood various types of streptococci in 84 per cent, and Gray[26] in 71 per cent of cases. Defense mechanisms convert the hemolytic streptococcus to less virulent types of streptococci, to staphylococci and to diphtheroid bacilli.[27] These dissociants are found consistently in the joints of arthritics.[28] Conversely, an exalted dissociation (from the weaker variants to the hemolytic streptococcus) takes place during exacerbations of rheumatic fever and arthritis,[28] particularly, as I have suggested in previous studies, following chilling, during storms and when the air is heavily ionized.[7, 27, 29, 30, 31]

5. *Geographical Variations in Incidence.* In areas where opportunity for chilling is great, rheumatic fever has a high incidence and the serum antistreptolysin titers of the population are correspondingly high.[32] Chilling predisposes to streptococcic colds, i.e., exacerbations of chronic sinusitis. Rheumatic fever may follow in a predisposed individual, heredity[18] being a factor in this predisposition.

6. *Seasonal Variations in Incidence.* Rheumatic fever reaches its peak incidence in the United States from January on the west coast to April elsewhere; in England, from November to January. I have never seen an explanation for this phenomenon and offer the factor of chilling to account for the seasonal (and yearly) variations in incidence of rheumatic fever.[33]

Glover and his associates[34] state that in England rheumatic fever is more prevalent in the cold, damp months of fall and winter. Temperatures drop to 50° F. at least two months earlier in London than in New York. In October, London averages 50° F., New York 56° F., and the west coast cities of Portland and Seattle, 54° F.

Although these temperatures do not differ greatly, the corresponding "effective temperatures" differ considerably due to strong winds and high humidity on the west coasts. Petersen and Mills have shown that chilling results from low temperatures combined with increased humidity (fogs) and constant winds. The earlier chilling on the west coasts of America and Europe probably accounts for the earlier peaks of rheumatic fever in both continents as compared with inland or east coast cities.*

OTHER SUPPOSED CAUSES OF RHEUMATIC FEVER

With the above correlations in mind, I believe that research in rheumatic fever might well be directed toward confirming or negating these contentions, rather than the following four unlikely causes proposed by some rheumatologists.

1. *Food Deficiencies.* Vitamin C deficiency and improper diet have been considered etiologic in rheumatic fever. Food factors are readily ruled out when one considers the poor diet of the Porto Rican and the absence of rheumatic fever in Porto Rico. The experience of Coburn, that Porto Ricans in New York City develop rheumatic fever and that rheumatic children from New York quickly get well in Porto Rico, rules out constitutional factors in these groups.

Coburn[42] writes: "Economic conditions in Porto Rico are such that there is a large population of the poor in San Juan who live crowded together in large families, with inadequate food. The standard of living is comparable to that of poor people in New York." Homer Swift[47] states: "If nutrition is a tremendously important factor, we shouldn't have so much rheumatic fever in our Armed forces, because they receive an excellent diet, and yet they are having a lot of rheumatic fever." It is likely that vitamin C deficiency is a result, not the cause of the disease (Keith and Hickmans; Sherwood).

2. *Virus as Cause.* Swift[48] objects to the virus theory on two counts: (1) Viruses do not produce fibrinoid degeneration as found in rheumatic fever and (2) no virus has definitely been discovered after 15 years' search.

*In northern California[38] and Oregon[39] the peak incidence of rheumatic fever is reached in January and February. In England the peak occurs in November,[37] in Scandinavia January, whereas away from the coast, as in Germany, the peak of cases is reached during March or April, as also in New England,[38, 39] New York City,[40, 41, 42] Philadelphia,[43, 44] Cincinnati,[45] St. Louis[4] and Minnesota.[46]

3. *Allergy as Cause.* Aschoff concluded that allergic reactions occur in rheumatic fever, but "to maintain that rheumatism and allergy are equivalent is fundamentally impossible." The term is often used too loosely. We know, for example, that scarlet fever is caused by the hemolytic streptococcus; "allergy" to the organism need not be invoked. In both rheumatic fever and scarlet fever, an incubation or prodromal period exists following initial activity of the hemolytic streptococcus and prior to the onset of symptoms.

4. *Endocrine Abnormality.* Recent research has established the value of cortisone and ACTH in the treatment of rheumatic fever.[49, 49a] This should not be construed to mean that deficiency of adrenal cortex causes rheumatic fever. The adrenal cortex is probably the most important defense mechanism against infection that man possesses. Adrenalectomy in animals lowers defense against infection more than any other known experimental procedure.[50] Injections of cortisone (and ACTH when the patient's adrenals are intact) replenish this defense and abort a variety of infections, including all types of pneumonia, iritis, etc.[51]

Streptococcal toxins from chronically infected sinuses readily attack glandular structures in the body through dilated capillaries[51a] of lowered resistance.[52, 53] Thus they may produce a cortical hypoadrenia.[54] In the same manner streptococcal toxins attack the thyroid, producing a hypothyroidism in many rheumatic children in the winter and spring.[55]

When cortisone is withdrawn from treatment, rheumatism and arthritis tend to recur. It would thus seem that cortisone affords good replacement therapy, but does not remove the cause of rheumatic fever.

TREATMENT

The most effective prophylactic and active treatment for rheumatic fever is unfortunately impractical in most cases, namely, residence in a tropical climate.[42] Sinusitis is least active in summer and in warm, moist climates. It is probable that the alpha streptococcus, basic in all pharynges and infected sinuses, does not readily change to the beta streptococcus in areas where chilling is absent. As Coburn states it: "In Porto Rico epidemic strains of the Strepto-

coccus hemolyticus find conditions unfavorable for the maturation of their natural life history."

For children who must remain in the temperate zone, successful prophylaxis has been obtained by oral penicillin[56] or intradermal injections of a proper streptococcic vaccine. The success by both methods of prophylaxis is probably due to inhibition of streptococcic activity in the nasal sinuses. Penicillin prevents the conversion of the alpha to the beta streptococcus,[27] as does a proper vaccine. Using streptococcus toxoid prepared from toxins of the hemolytic streptococcus, Wasson and I markedly reduced the number of recurrences of rheumatic fever over a period of eight years.[57] Recently, Kurtz,[58] using a similar vaccine, confirmed our work. He noted 56 per cent recurrences (major and minor) in the controls as against 7 per cent recurrences in children given alum-precipitated toxin of the hemolytic streptococcus.

For effective prophylactic and active treatment of rheumatic fever, infected sinuses should be drained. Briefly, this is accomplished as follows:

1. Elevation of the head and avoidance of prolonged recumbency as previously described.[59] The usual advice, "bed rest," without further qualification as to the head-up position, permits accumulation of pus in the sinuses, circles and puffs under the eyes[59, 60] and progressive enlargement of the cervical nodes.[59, 61]

2. Use of proper nose drops or a benzedrex inhaler® twice daily, followed by hot wet towels to the face. Ephedrine sulphate, 1 per cent, in normal saline solution, tends to open the ostia of the sinuses, while moist heat to the face, as advocated for many years at the University of Michigan, by Canfield and later by Furstenberg, helps to drain purulent secretions under tension. Morning headaches are thus effectively relieved.

3. Avoidance of chilling. Chilling permits accumulation of purulent secretions in the sinuses because of the resulting activity of the streptococcus. The rheumatic child should wear sufficient clothing, avoid drafts, wet feet and wet hair. No showers should be taken before bedtime unless the hair is protected against wetting.

4. Allergens should be sought and avoided, since they tend to produce congested sinuses.

5. Fatigue should be avoided, since it tends to lower resistance against infection.

DISCUSSION

Wasson and I examined 100 ambulant rheumatic children at the New York Post-Graduate Hospital and reported that, after 1,300 examinations (13 per patient), every child was found to have an active chronic sinusitis, a diagnosis based on numerous signs.[19, 61] We concluded that chronic sinusitis "may be important in its etiologic relation to the rheumatic process."[19] However, others had already emphasized this relationship.[62-66] Marriott[67] stated that "sinus infections are usually observed" in patients with articular rheumatism and Watson-Williams[68] remarked that often cases of recurrence of rheumatism are really due to unsuspected sinus disease, a point borne out by our study.

Rheumatic fever exists only in man and may be explained by his posture which favors the development of chronic sinusitis (Cullom). No other animal walks on his hind legs and lies in the recumbent position. The position of the head in dogs and horses, for example, is favorable for drainage when a cold develops. In children, on the other hand, by placing them in the supine position, infected nasal secretions readily enter the sinuses where bacteria tend to perpetuate themselves for life. When the child is up and about, gravity holds a residuum of pus in the most dependent sinuses (antra). Secretions reaching the ostium are usually sniffed, hacked and swallowed, maneuvers never encountered in other animals.

It is pertinent to ask, Why do only a few of the innumerable children with sinusitis develop rheumatic fever? Two factors are important: (1) Heredity, as emphasized by May Wilson, is one factor. The child without such heredity is less likely to develop the disease. (2) More important is pus under tension in the sinuses. Without such tension, cervical adenitis does not develop and toxins of streptococci are not likely to invade the tissues. One can readily follow the degree of cervical adenitis at the onset of rheumatic fever and during convalescence, noting the diminution in size and tenderness of the cervical glands. At the same time one can note the marked tenderness of the sinuses at the onset and its subsidence during convalescence. I have consistently found this correlation.

Rheumatic fever, then, occurs when large amounts of streptococcal toxin enter the circulation from pus under tension in the

sinuses, particularly after a "cold." At this time the sinuses are always tender to palpation, often exquisitely so (Fig. 1). The toxins cause enlargement of, then pass through, tender cervical nodes (Fig. 2).

Many experiments to produce rheumatic fever in animals have proved futile. However, one which established a chronic infection in the subcutaneous tissues by using pledgets of cotton soaked in cultures of streptococcus viridans obtained from persons with rheumatic fever, was successful in producing lesions in rabbits and in dogs essentially like those of rheumatic fever.[69] In recent experiments, Murphy and Swift[70] injected rabbits intracutaneously every month or twice a month with minute doses of streptococcus viridans and obtained clinical symptoms resembling rheumatic fever in man; cardiac lesions also resembled those of rheumatic heart disease as seen in human subjects. In both these experiments, human rheumatism was simulated by permitting the continued absorption of streptococcus toxins, the immediate pathogenic agent of rheumatic fever.

In man, chronic sinusitis is the only consistent focus for streptococcus toxins under pressure. Rheumatic pains result when they are forced from the sinuses into the general circulation.

In the past 18 years, I have seen rheumatic fever periodically in new patients, but rarely in patients previously under my care. I believe the reason for this lies in the fact that I have always made it a point to note the status of the nasal sinuses of every child I have examined, and prescribe treatment for all with active sinusitis. When rheumatic fever was observed and the complicating sinusitis treated, fever, pain and other symptoms of rheumatic fever subsided rapidly. Treatment of chronic sinusitis was continued indefinitely, and found to be an effective means of prophylaxis against rheumatic recurrences in several hundred rheumatic children.

CONCLUSIONS

Rheumatic fever is invariably caused by toxins of the hemolytic streptococcus located in purulent exudates under tension in chronically infected sinuses, accounting for sinus tenderness and enlarged cervical nodes.

Usually following chilling of the body, alpha streptococci in infected sinuses dissociate into hemolytic (beta) streptococci and

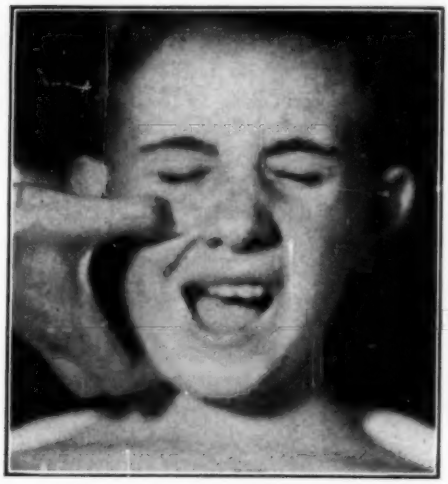

Fig. 1. Severe antral tenderness at onset of rheumatic fever.

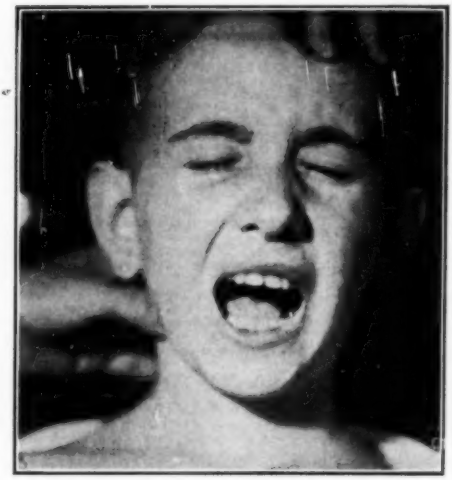

Fig. 2. Severe tenderness of cervical nodes (despite previous tonsillectomy).

produce the respiratory infection known to precede the rheumatic attack. The rise in antistreptolysin titer preceding the attack signifies a humoral response to the hemolytic streptococcus. During convalescence defense mechanisms in the body convert the hemolytic streptococcus to its weaker dissociants which are found in the sinuses and frequently in the blood and joints of rheumatic individuals.

Treatment of the complicating sinusitis causes rapid subsidence of rheumatic fever. Reccurences are prevented by continued daily treatment of chronic sinusitis, such as the use of proper nasal astringents followed by hot wet towels to the face twice daily, and by elevation of the head during recumbency. Effective prophylaxis may also be obtained by oral penicillin and by the use of proper streptococcus vaccines, both methods preventing dissociation of alpha to beta streptococci in the sinuses.

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FAMILIAL IDIOPATHIC METHEMOGLOBINEMIA. (Lancet, London: 1: 935, April 28, 1951). The authors report two cases of familial idiopathic methemoglobinemia in children aged 3½ years and 6 years respectively. Both were cyanotic from birth, and one was thought to have congenital cardiac disease. Both developed normally, however, and showed no dyspnea. No other available members of the patients' families were found to have methemoglobinemia. This supports the belief that the disease is inherited as a recessive character. The erythrocytes of these patients showed an abnormally low capacity to reduce methemoglobin in the presence of glucose or lactate and an abnormally low activity of diaphorase I (coenzyme factor I). This defect in the reducing system of the cells is thought to be responsible for the symptoms in this disease. Since there is a continuous slow oxidation of hemoglobin to methemoglobin in the blood, any decrease in activity of the reducing systems of the erythrocytes permits an accumulation of methemoglobin. The patients reported on were treated successfully with methylene blue and ascorbic acid.—*Journal A. M. A.*

COLD WEATHER AS A FACTOR IN THE EPIDEMIOLOGY OF GRIPPE AND THE COMMON COLD

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It is generally believed that one or more filtrable viruses are concerned in the etiology of grippe (or influenza) and the common cold.[1, 2] Dochez and associates[3] have also noted the effect of viral infections in lowering individual resistance to ordinary pyogens. (Filtration studies have indicated that the viruses of grippe and the common cold are extremely small; this is significant since diseases due to small viruses have not yet been found amenable to antibiotic or chemotherapeutic measures.[3])

Exposure to viral agents, however, does not necessarily provoke the clinical syndrome of grippe or colds. In recent years there has been evidence that conditioning factors may often be necessary to "trigger" the patient's reaction to the potential pathogen. Especially in endemic areas, it seems essential that there be a lowering of resistance before enough damage is incurred by the respiratory epithelium to permit invasion by the pathogenic organisms.[4]

Prominent in numerous accounts of the origin of respiratory illness is the factor of exposure to severe cold. Today it is widely held that cold weather may predispose the individual to colds because of its adverse effect on the individual's resistance. This is further borne out by seasonal variations in the occurrence of colds and other respiratory conditions. In addition, the positive influence of cold weather on the incidence and severity of allergic manifestations, and the fact that allergic persons show an increased susceptibility to the common cold seem to indicate a correlation between low temperatures and respiratory disease.[5]

With these considerations in mind, it was decided to observe a large series of children with a view toward ascertaining the relationship between cold weather and the occurrence of acute illness and secondary infection—and to attempt to analyze our findings with regard to the probable physiologic mechanisms involved.

METHOD

Inasmuch as February and March are usually cold months, every case of acute illness during these months was noted and the first

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day of illness charted on a graph (Fig. 1). During 1951, February and March were comparatively mild, but fortunately five isolated days of subzero temperature occurred, and these were adequately spaced to permit repeated analysis of their relationship to the time of onset of illness.

The illnesses included acute respiratory disease (the term "disease" is used in order to suggest biochemical disequilibrium,

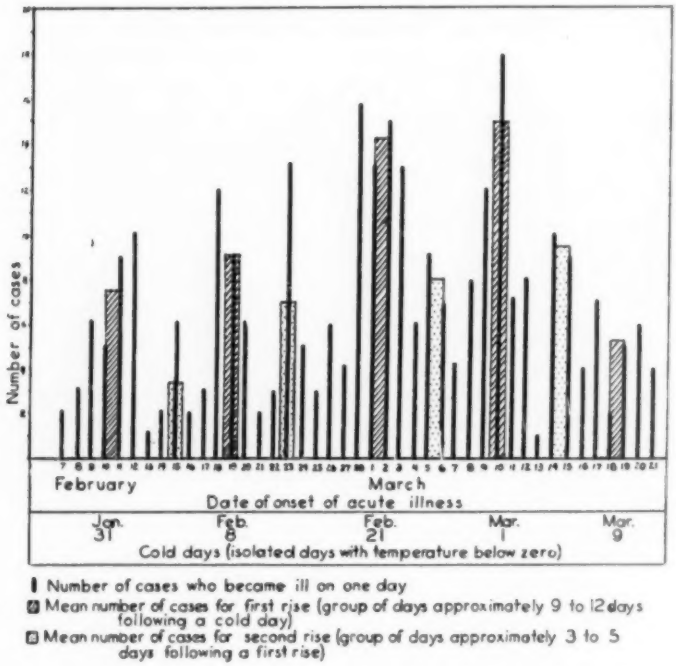

Fig. 1. Number of cases with onset of illness by date, and mean number of cases for groups of days following cold days.

rather than "infection," which implies specific injury resulting from bacterial invasion and tissue destruction); 24–48 hour fever, acute gastrointestinal disease characterized by recurrent abdominal pain, vomiting, and/or diarrhea. Under "respiratory disease" were grouped coryza, croup, acute pharyngitis, acute laryngitis, acute tracheitis and acute tracheobronchitis.

Many children were seen the first day or two of their acute illness, at which time no specific clinical infection could be detected. Several children were examined at the time of secondary *infection*, which most often appeared clinically three to five days after the onset of an acute illness (Fig. 2). The infections included otitis media, nasopharyngitis, follicular tonsillitis, laryngitis, bronchitis, lobar pneumonia and primary atypical pneumonia; some children developed vomiting and/or diarrhea three to five days after the

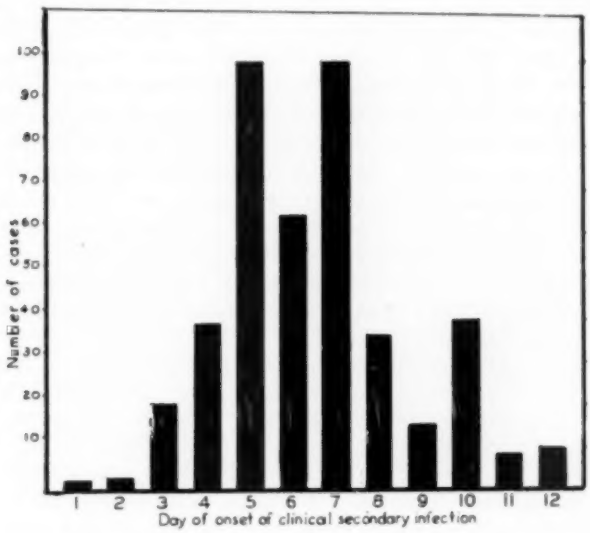

Fig. 2. Number of cases by day of onset of illness.

onset of respiratory disease. In still others, whose initial illness was characterized by gastrointestinal dysfunction, the clinical symptoms persisted or became exacerbated, indicating localization of the infection in the gastrointestinal tract.

RESULTS

1. Approximately 8 to 12 days after any day of subzero temperature, there appeared a sharp and sustained rise in the incidence of acute illness.

2. A second increase in the number of cases of acute illness was noted three to five days after each initial peak.

3. Each successive subzero day was associated with a subsequent increase in the number of sick children.

4. Following final exposure to subzero weather, the incidence of acute illness gradually declined to endemic levels.

COMMENT

The exact manner in which drastic fall in temperature causes acute illness is not yet known. Several explanations have been offered to account for the development of the common cold, cold equivalent (gastrointestinal dysfunction), or grippe—all of which are merely different forms of the same acute manifestation of disease. Four possible causal factors may be involved: (1) cold trauma may affect the delicate exposed tissue of the respiratory tract like a first degree burn (cf. the "lung chill" noted in the Russian literature[6-8]); (2) cold possesses antigenic properties which may initiate a sensitization reaction in susceptible persons[9]; (3) cold stimulates the production of auto-antigens or haptens which establish a sensitization reaction[10]; and (4) cold lowers the resistance of the individual,[11] permitting resident potential pathogens or their mutants to set off an anamnestic reaction conducive to biochemical disequilibrium.[12, 13]

This biochemical disequilibrium seems to offer the best explanation for the occurrence of acute illness, often without apparent infection, after exposure to extreme cold.

THE ANAMNESTIC REACTION

The anamnestic reaction is interpreted as a period of rapid production of large quantities of antibodies by a previously sensitized animal or person in response to minute antigenic stimuli.[14, 15] This reaction creates an almost instantaneous demand for adequate quantities of labile amino acids necessary to the synthesis of specific antibody globulin. When dietary sources cannot meet the emergency requirements, plasma amino acids are monopolized for the purpose. Reserve protein (albumin) cannot be utilized for immediate amino acid synthesis.[16] (Following any severe stress factor, intercellular as well as reserve proteins are "burned" and those amino acids not metabolized for energy are excreted. Conversion and protoplasmalysis[16] takes place after the fourth day and not until then does synthesis of functional protein become apparent.) Meanwhile, the tissues are subjected to an acute insufficiency of one or

more specific nutrients which may affect the more labile parts of the organ systems, such as the vascular bed; or the functional systems, such as reflex activity or gastrointestinal motility. In other words, there arises an acute amino acid insufficiency for those building blocks necessary to maintain the "dynamic state" or nitrogen integrity of essential tissues.[17] In addition, new metabolites, histamine and associated H substances may cause direct injury to tissue.

CAPILLARY PERMEABILITY

Aikawa and Harrell[18] have demonstrated an increase in the thiocyanate space and a decrease in the blood volume in serum sickness experimentally produced in rabbits by the injection of fractions of human plasma. This observation can be interpreted as indicating an increase in permeability of the vascular tree, permitting the progressive loss of crystalloids and colloids.

STRESS REACTIONS

Serum sickness and the anamnestic reaction are stress situations or alarm reactions to which the body reacts in a compensatory or adaptive manner. They stimulate the adrenal via Cannon's homeostasis or Selye's adaptation mechanism, with ultimate liberation of pressor-depressor substances which can cause vasoconstriction.[19]

A basic mechanism for the participation of the adrenal in the pathogenesis of reaction to stress has been established by Selye[20] in his "General-Adaptation-Syndrome." The body reacts to "cold" as it would to any severe stress situation. Stress increases the secretion of adrenalin which stimulates the pituitary and in turn the adrenals. Adrenocorticoids increase the release of specific cellular antibody globulin.[21] When humoral antibodies are adequate, tissue cells remain refractory to the antigen-antibody response. Synthesis of antibody globulin obeys the laws of protein synthesis.[16] By virtue of the fact that immediate synthesis of specific antibody globulin from reserve protein is impossible, available dietary amino acids as well as plasma amino acids are monopolized at the expense of other tissues which require them for normal metabolism.

RESUMÉ

Compensatory vasoconstriction may be responsible for the retention of body heat and the production of fever. Heat of chemical reaction; biochemical disturbances due to exhaustion or over-

stimulation of one or more defense organs (stress reaction)[20]; release of H substances; inflammation; and allergic manifestions[18]—one or more of these processes may contribute to the symptomatology of the common cold, cold-equivalent or grippe.

SECONDARY INFECTION AND ANAMNESTIC REACTION

The secondary rise in acute illness three to five days after the initial onset may be explained on the basis of the variable and intermittent activity of the body's defense mechanism.[22] A general level of immunity high enough to provide protection against a specific infectious disorder cannot always be achieved through a single experience with a newly acquired antigen. In many subjects, *repeated* anamnestic reactions are necessary to reinforce existing immunity.[23] At a midway point, partial immunity may inhibit trivial infection. Potential pathogens may then act as specific antigens to initiate a brisk excitation of the defense mechanism.[15] The patient reacts as he would to any foreign protein, presenting symptoms which can be described as an accelerated modified serum disease. Thus, the anamnestic reaction, which *substitutes* for definite infection, gives rise to the clinical syndrome known as the common cold, cold-equivalent or grippe. The type and degrees of reaction vary from person to person, and in the same individual from one time to another.

As shown by our clinical studies, a sensitization reaction may occur 8 to 12 days after initial exposure to cold weather, without at first presenting signs of true infection.

A low grade infection, according to Locke,[13] is one which occurs only in animals or persons that have been rendered susceptible by some physiologic handicap (idioblaptic allergy) "low grade infection gains a foothold because of impairment in the ability of the natural defense mechanisms to function." Diminished efficiency of the natural barriers of defense provides a portal of entry which in the absence of adequate local specific antibody immunity permits invasion by resident potential pathogens; secondary infection becomes clinically apparent three to five days after onset of the primary acute illness (the common cold).

Bacteria increase in virulence as they are transmitted from person to person. In some individuals, atypical or latent infection substitutes for typical clinical infection.[14] These persons are carriers who spread droplet infection to more and more of the popu-

lation, increasing numbers of whom harbor organisms of increased pathogenicity. When a day of severe cold arrives, the cold acts to lower the resistance of these individuals, and there is a consequent rise in the number of sick persons after each succeeding subzero day. Increasing immunity and eventual termination of cold weather lead to a reduction in the incidence of acute illness to an endemic level.

SUMMARY

1. A large series of acute illnesses localized in the respiratory and/or gastrointestinal tract has been analyzed with special reference to their frequency and time of occurrence in relation to isolated days of subzero temperature.

2. An interpretation of the data is offered in terms of anamnestic reactions substituting for clinical infection. These are held to provoke the clinical syndrome of common colds, cold-equivalent or grippe as a manifestation of biochemical disequilibrium. In some individuals, clinical infecton may develop three to five days later; in others, partially immune, an anamnestic reaction may develop in response to newly acquired potential pathogens.

CONCLUSIONS

Evidence has been presented indicating that extreme cold is a potent stress factor which brings about acute illness in the form of the common cold, cold-equivalent or grippe 8 to 12 days following initial exposure with possible secondary infection three to five days later. Grippe is thus a noninfectious syndrome precipitated by stress factors as well as infectious agents; these are not necessarily of any one specific type. Constitutional heritage as well as varying degrees of immunity in different individuals account for the variability in the clinical picture. As individual immunity progresses, there is increased likelihood of anamnestic reactions substituting for true clinical infection. Finally, as the provocative stress factor of cold is removed, the occurrence of acute illness gradually diminishes to endemic levels.

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CRANIOTABES. (Ugeskrift for Laeger, Copenhagen, 112: 1326, Sept. 21, 1950). Blom reports that of 662 children examined at two children's welfare stations 83 (12.6%) had craniotabes. The results support the assumption that craniotabes is not of rachitic but is of physiological nature. Prophylactic administration of cod liver oil to mothers and children did not prevent craniotabes but prevented rickets. Craniotabes is thought to be an osteoporosis due to high growth intensity. The parietal bones are most commonly affected, perhaps as the place of least resistance, since they are exposed for the longest time to the greatest intrauterine and postnatal pressure.—*Journal A.M.A.*

SCLEREMA NEONATORUM*

Report of Case

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Sclerema neonatorum was first described by Underwood in 1784, and since then has been reported sporadically.[1] It is an unusual condition found in premature and debilitated newborn infants, in which the greater part of the body assumes a cadaveric or "frozen" appearance.[2, 3]

This paper presents a case of sclerema in a premature infant.

CASE REPORT

This two-pound one-ounce female infant, J.V.S., was prematurely born but was alert and cried spontaneously. Her respirations were a little irregular at first, and she was placed in a heated incubator, given parenteral vitamin K and continuous oxygen. After 24 hours she was placed on dropper feedings of glucose water and given small parenteral clyses of glucose and saline in order to maintain her hydration. The respirations, however, remained shallow. On the third day after birth, a dilute low fat high protein formula (Dryco) was started by dropper, or, when intake was insufficient, by gavage. Body heat remained good in the incubator and, although she developed a few loose bowel movements following the milk feedings, these ceased spontaneously within several days, only to recur at variable intervals. Eleven days after birth her weight was one-pound fifteen-ounces, and she seemed to be doing well.

From this period to her seventeenth day she was continued on oral feedings and given parenteral fluids only as needed. The diarrheal stools improved, but she tended to regurgitate many of her feedings, and remain hydrolabile. She occasionally evidenced cyanosis, and this, plus her diarrhea, vomiting, rather poor weight gain and somnolence, were suggestive of temporary hypoadrenalism.[4] Substitution therapy, consisting of a half gram of salt daily and adrenal cortex parenterally, were tried without altering her course.

On the seventeeth day she started to become rigid. This rigidity began in the lower extremities and spread slowly over the next three days, to involve the abdominal wall, chest, back mucles and

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face in an ascending manner. The skin appeared marble-like, rigid, cold and inelastic, and the superficial skin did not move readily over the subcutaneous tissues. The tissues of the face as well as the abdomen and extremities were "board-like" and did not pit to pressure, and there was no evidence of edema. The infant could be picked up by an extremity and the entire body could be lifted in this manner.

By the time this muscular rigidity reached the face, the infant appeared unable to swallow, and respirations had become labored. She could not move her rigid extremities well, but did cry weakly. There were no seizures and no neck rigidity, and the anterior fontanel remained soft. Her temperature, which had been maintained, fell to subnormal levels and could not be elevated despite external heat. Gavage feedings were given entirely because the mandible seemed to be fixed in a partially open position.

Three days after the start of these signs alpha-tocopherol was initiated but did not alter the course, and the infant died nineteen days after birth.

Laboratory. The blood count revealed 14,900 W.B.C. per cmm. with 34 per cent neutrophils, 53 per cent lymphocytes, 7 per cent monocytes and 6 per cent eosinophils. There were 4.8 million R.B.C. per cmm. and 9.6 grams of hemoglobin per 100 cc. The smear was not abnormal. Stool culture, taken during the diarrheal episode, revealed no enteric pathogens.

Post-mortem examination was not permitted.

DISCUSSION

Sclerema neonatorum (sclerema adiposum) is to be differentiated from subcutaneous fat necrosis, also properly called sclerema, and scleredema neonatorum.

Sclerema of the sharply circumscribed type is more correctly called subcutaneous fat necrosis, as the areas of induration are sharply outlined and are attached to the skin but not to the deeper tissues. These areas, usually symmetrically situated over the bony prominences of the body, such as the tibiae, become evident within the first few weeks of life and disappear after three to four months. They occasionally soften and become cystic.[2, 3, 5] These children are usually full term and otherwise healthy.

Scleredema is usually not confused with true sclerema since the

former is often present at birth, usually affects the dependent portions of the body, and pits on pressure.[6]

Sclerema neonatorum, a condition of unknown etiology, usually appears suddenly on the third or fourth day of life or anytime during the first few weeks of life in premature or weak debilitated infants. Sometimes it appears at a little later age in marasmic infants with gastroenteritis and dehydration or other severe infantile diseases.[5] It is usually a terminal condition and the term "preagonic induration" has been suggested.[2] Only a few survive over ten days once this progressive condition starts.[6]

The lesions are revealed first in the subcutaneous fat of the lower extremities, usually on the calves, and then rapidly spread upward to involve the entire body surface, especially the buttocks, back and cheeks. The palms of the hands, soles of the feet, and scrotum, where fat is absent, are uninvolved.[5] The skin is smooth, reddish, purplish or mottled and is stony hard and cold to the touch and does not pit on pressure. It appears to be adherent to the underlying tissues, and has been aptly described as cadaveric, frozen or hidebound.[6] The severest cases are unable to move, due to joint involvement.[3, 5, 7] In a few cases there is recovery, but most of the infants die within ten days after the start of the disease. The body temperature becomes subnormal, and there is somnolence, anorexia, and occasionally atelectasis. Pulse and respiration become progressively slower until death ensues.[3]

Predisposing factors to this unusual condition are prematurity, asthenia, chilling, and possibly prolonged labor, or obstetrical trauma. Langer, as quoted by McIntosh, believes the pathogenesis apparently depends on the lower percentage (65 per cent) of oleic acid in an infant's subcutaneous fat, as opposed to 86 per cent in adults, the melting point of the infant's fat actually being higher than the normal body temperature.[2]

Pathologically, the process is essentially a necrosis of the fat cells and an infiltration of epithelioid and giant cells. There is often an increase of the trabeculae in the subcutaneous tissues, with deposits of crystals of natural fat and occasionally calcium.[3, 5]

Treatment is supportive since the immediate cause is unknown. External heat, thyroid, and dessicated pancreas have been suggested.[3, 6, 8] Gerloczy has recently suggested using alpha-tocopherol.[7] In a series of 38 cases he reported 36 recoveries, all ap-

parently after an intense diuresis, but whether he was treating scleredema or true sclerema is not entirely clear.

SUMMARY

1. Sclerema neonatorum is an unusual condition occuring commonly in premature infants, and is usually fatal.

2. A fatal case of sclerema is reported in a two-pound female infant.

3. The condition is one of progressive ascending induration involving the subcutaneous fatty tissue.

4. Treatment is supportive, but alpha-tocopherol seems worthy of further investigation.

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PSEUDO-ORCHITIS IN CHILDREN. (Revista Española de Pediatria, Zaragoza, 7: 45, Jan.-Feb. 1951). Fernández discusses pseudo-orchitis in children and describes eight cases. The main causal factors of the syndrome are (1) torsion of the spermatic cord, (2) torsion of the sessile hydatid of Morgagni, and (3) the idiopathic hemorrhagic infarct of the testicle. Although the symptoms correspond distinctively to the variety of the anatomic component involved, the diffentiation of some forms from others is difficult. The author establishes two phases in the differential diagnosis. In the first phase pseudo-orchitis is differentiated from acute infections, allergic, chronic, tuberculous, and syphilitic orchitis, whereas in the second phase the disease is differentiated from (1) pyogenic nonspecific, tuberculous, acute syphilitic, and chronic epididymitis and (2) epididymis and testicular tumors, local inflammation, and other local diseases. The treatment consists of early surgical detorsion of the testicle and orchiopexy of the testicle to the vaginal tunica of the testicle.—*Journal A.M.A.*

BACILLARY DYSENTERY

Report of Case

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and
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St. Louis.

Bacillary dysentery is a disease characterized by fever, toxicity, tenesmus, abdominal pain and the passage of frequent stools containing mucus, blood and pus. The positive diagnosis depends upon the isolation of the organism from the stool.

The authors report a typical case of bacillary dysentery occurring in a four-year-old child.

CASE REPORT

This four-year-old white male child was admitted to the hospital on July 20, 1951 with a complaint of fever, vomiting, and diarrhea of three days duration. For the three days prior to admission the temperature ranged from 102° to 104° F.; on the day prior to admission the child passed thirty-five bloody-mucoid stools.

The past history was not contributory in-so-far as the present illness was concerned.

Physical examination revealed a well developed and well nourished four-year-old male who appeared to be acutely ill and toxic. His temperature on admission was 104.4° F., pulse rate 112 per minute, and respiratory rate 48 per minute. The skin was hot and dry, the cheeks flushed and the lips cherry-red. The tonsils were enlarged and moderately injected. Examination of the chest was negative. The abdomen was soft and flat with generalized tenderness. Examination of the extremities was negative.

On admission the red blood count was 5.76 million; the hemoglobin 15.4 grams; the white blood cell count 8,700. The differential white blood cell count revealed 2 juvenile forms, 32 stab forms, 23 segmenters, 36 lymphocytes, 2 monocytes and 3 smudge cells. The CO_2 combining power of the blood on admission was 15.8 milliequivalents. The stool examination revealed mucus, pus and blood.

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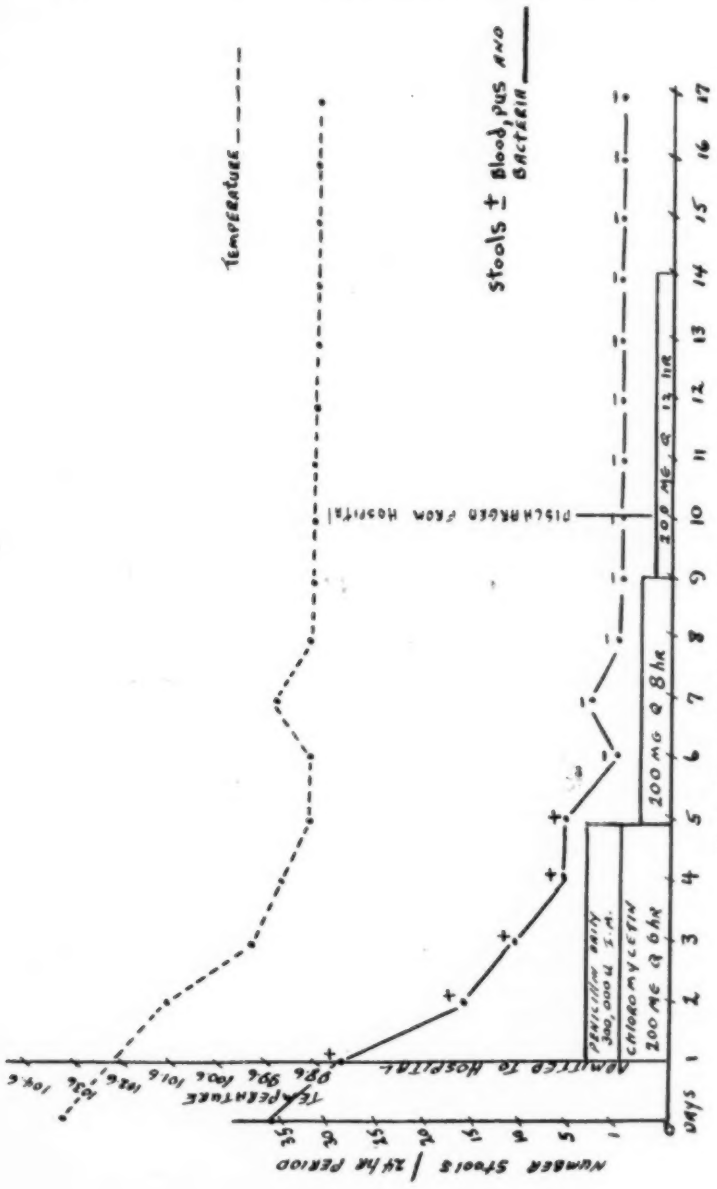

Fig. 1. Reveals hospital course and response to treatment.

The impressions on admission were (1) acidosis and (2) dysentery.

The treatment was directed toward correcting the acidosis by parenteral fluids and controlling the diarrhea with chloromycetin and penicillin.

Further laboratory examination of the stools revealed pus and blood to be present for the six days following admission. Cultures of the stool revealed a Shigella dysentery variety Flexner. The stools remained positive for the six days following admission. Agglutination tests revealed a titer of 1:640 at the end of one hour and 1:2,580 on standing for twelve hours.

The red blood cell count fell to 3.04 million and the hemoglobin to 11.7 grams on the seventh hospital day. The patient was given a transfusion of 200 cc. of blood. Following this, the red blood cell count was 4.2 million and the hemoglobin was 12.5 grams. Fig. 1 summarizes the chemotherapy and the progress of the patient during his illness.

DISCUSSION

Many reports have appeared in the literature to indicate that sulfanilamide derivatives are the drugs of choice in the treatment of dysentery caused by Shigella organisms. From 1940 through 1946 there are reports of treating dysentery with poorly absorbed sulfonamides and sulfonamides that are readily absorbed.[1-7] The use of sulfonilamide derivatives as the treatment for Shigella dysentery is widely accepted; however, Mazursky[8] has pointed out certain disadvantages and limitations to the use of these drugs. Briefly, these disadvantages are as follows:

(1) Certain patients develop allergic manifestation to sulfonamide drugs.

(2) There is the possibility of drug toxicity.

(3) Sulfonamide resistant strains of Shigella may be present.

(4) In cases where dehydration has resulted from the diarrhea, it is dangerous to initiate such therapy until the dehydration is corrected by parenteral fluids.

For these reasons Mazursky treated three cases of Shigella dysentery (Sonne) with chloromycetin. It was the reported success with these cases that prompted the authors to treat this patient with chloromycetin. The clinical response of our patient was prompt

and gratifying. Weekly stool cultures for one month following the discontinuing of chloromycetin have remained negative.

SUMMARY

1. The authors report a case of Shigella dysentery of the Flexner variety, treated with chloromycetin.

2. A brief discussion to point out the advantages of chloromycetin therapy over sulfa therapy is included.

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PINK DISEASE IN OLDER CHILDREN. (Medical Journal of Australia, Sydney, 1: 353, March 10, 1951). Cheek believes that pink disease (acrodynia) may be a manifestation of adrenal dysfunction either primary or secondary to renal disturbances. He found low levels of plasma sodium and urinary chlorides in his acute cases and observed that these abnormalities persisted in some children who were under stress after the typical symptoms of photophobia, hyperhidrosis, irritability, swelling and redness of the hands and feet, and skin rashes had disappeared. Eleven such children between the ages of 2 and 7 years showed the syndrome of the nervous child and exhibited allergic manifestations with eosinophilia. Recovery followed the administration of sodium chloride alone in the mild cases (plasma sodium level 300 mg. per 100 cc.) and followed the administration of 5 mg. of desoxycorticosterone daily in the severe cases. Salt alone did not restore normal osmotic relationships in most cases. There was no abnormality of the blood epinephrine content in 18 children with pink disease. The author speculates that some toxic or photodynamic agent may injure the renal tubules in this disease, altering electrolyte excretion and placing a strain on the adrenal because of its role in maintaining homeostasis.—*Journal A.M.A.*

PEDIATRICS HALF A CENTURY AGO

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

DECAPSULATION OF BOTH KIDNEYS (EDEBOHLS' OPERATION) IN A BOY NINE AND ONE-HALF YEARS OLD*

REPORT OF CASE

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AND

H. W. CUSHING, M.D.

Boston.

The boy entered the Children's Hospital, Boston, September 11, 1902. Family history negative. He was reported to have had measles three times, and to have been subject to tonsillitis. He was also reported to have had diphtheria and typhoid fever in the year previous, for which he was treated in the hospital. He was said never to have had rheumatism or scarlet fever. During his attack of typhoid in the previous year, the urine was reported to have been as follows: Color high; sp. gr. 1,022; reaction acid; sugar absent; albumin slightest possible trace.

Three or four days before his entrance to the hospital it was noticed that his abdomen began to be enlarged, and this was followed by swelling of the legs and then of the face. At this time there was noticed no change in the urine as to color and amount. He was said to have had dyspnea on exertion for some time previous to his entrance to the hospital. Had had no headache and no vomiting, but some dizziness at times. He was well developed and nourished; expression bright; skin clear, but of a pasty color; throat and tongue normal, but pale; teeth decayed; no enlargement of the lymph nodes. He had edema of the face and abdominal walls, and marked edema of the legs. The pupils were equal and reacted normally. Lungs were normal. Examination

*Read before the fifteenth annual meeting of the American Pediatric Society held at Washington, D. C., May 12-14, 1903.

Reprinted from ARCHIVES OF PEDIATRICS, 20: 561-569, August 1903.

of the heart showed no increased cardiac area and clear sounds, excepting second sounds which were strongly accentuated. The abdomen was somewhat distended, but not tense and no ascites was detected. The blood showed: hemoglobin 50 per cent; leukocytes 6,700.

The urine was smoky; reaction acid; sp. gr. 1010; albumin one-eighth to one-quarter per cent; bile and sugar absent; the sediment showed many hyaline and many granular casts with blood and renal cells adherent; a few fatty and epithelial casts; many round cells, often fatty; leukocytes free and in clumps; a few decolorized red corpuscles and a few squamous epithelial cells. Considerable free fat.

During the next three months the boy varied in his symptoms, sometimes growing better and sometimes worse. During this period he had at times considerable edema and a large amount of ascites for which he was tapped three times. The amount of urine also varied considerably from about 300 cc. to about 1,800 cc. The amount of albumin varied from one-eighth to one-quarter per cent. During this time repeated examinations of the urine showed no marked difference from that found at entrance. The summary of the condition of the urine up to the time the child was transferred for operation is as follows: Color was at times pale and at times smoky; sp. gr. was about 1,010; the amount passed in twenty-four hours varied from 400 cc. to 800 cc.; at one time shortly after entrance a larger amount was passed, reaching 2,500 cc.; the amount of albumin was fairly constant from one-eighth to one-third; the amount of urea excreted in twenty-four hours varied from five to ten grams; the sediment showed at all times very numerous casts both hyaline and granular, with renal cells and fat adherent; fatty and epithelial casts were usually present in smaller numbers, and at one time very highly refracting casts were noticed; fatty degenerated epithelium and free fat were constantly present in considerable quantities; renal cells were constantly numerous; the amount of blood in the sediment varied, at times there were many red corpuscles, free and adherent to the casts, and at others almost none.

The boy was transferred to the surgical department on December 28, three months after entrance, and was placed under the care of Dr. H. W. Cushing. The following are the subsequent notes of the case:

His condition when coming under Dr. Cushing's care was that of a patient suffering from advanced parenchymatous nephritis. There was edema of the face, also of the back and of the external genitals, and marked edema of the lower extremities. The examination of the chest showed the heart's action somewhat irregular, rate 108, the cardiac dullness somewhat increased to the right. The lungs showed dullness and flatness in the lower lobes dorsally, especially at the bases, and medium and fine moist râles. The skin was very white. There was slight cyanosis of the extremities. The abdomen was distended, the circumference at the navel was 31 inches. The percussion was flat except in the umbilical region, and contained 4,220 cc. of fluid. There was occasional nausea and vomiting. The urine was diminishing in amount. From 1,000 cc. in twenty-four hours it had decreased to 480 cc. on December 29. The specific gravity was rather low, 1,010; the amount of albumin varied from one-eighth to one-third per cent; the urea varied from five to nine grams in the twenty-four hours; the sediment contained hyaline, fine granular, granular and fatty casts and fatty renal cells in abundance. The patient's general condition was growing steadily worse in spite of several months' careful treatment.

On January 1, 1903, Dr. Cushing decapsulated both kidneys. The duration of the operation was fifty minutes for the left side and thirty-five minutes for the right. Previous to this procedure 4,220 cc. of a slightly opalescent fluid, odorless, with neutral reaction, a specific gravity of 1,011 and a slight trace of albumin was removed from the peritoneal cavity.

The anesthetic was ether, preceded by nitrous-oxid. The technique of the operation was the usual one. The operation was more difficult than the average case on account of the edema of the dorsal tissues and the inability to deliver the kidney outside the incision of the skin. The decapsulation had to be done in the depth of the wound. The kidneys were enlarged; the fibrous capsules were not adherent; the denuded surface was matted with yellowish-white areas alternating with injected ones; the cortex was quite friable. No especial cicatricial depressions of the surface were noted. The patient bore the operation well. The amount of ether inhaled was seven ounces. The pulse rate was 120 during the manipulation of the kidney, generally 100 to 110 at other times. The temperature fell to 94° F., three hours after the operation,

and rose to 99° F., four hours later. For the next seven days it averaged 101° F.

The first act of micturition occurred five hours after the operation, the amount being 30 cc. During the first twenty-four hours the amount was 62 cc. It was slightly pale; very acid; urea 0.39 grams; albumin one-seventh per cent; the sediment contained numerous hyaline, finely granular and fatty casts, fatty renal cells and compound granule cells, leukocytes and epithelial casts; a few fibrinous casts and cholesterin crystals. There were more blood globules than in the previous specimens. The ratio of urine to the total amount of fluid ingested was 1 to 6.

There was distinct thirst after the operation, but the patient said he felt much more comfortable than before. The headache had disappeared, also the nausea. The edema also began to diminish at once.

The patient was temporarily relieved and lived until January 19, on which day he died suddenly, with symptoms of acute pulmonary edema and cardiac exhaustion, eighteen days after his operation. The improvement noted immediately after the operation continued to January 8, or 9, and the condition seemed to indicate a favorable result up to that time. The patient was cheerful and quite comfortable. The edema had disappeared except in the legs and feet where it was much less.

The urine increased in amount from 85 cc. in twenty-four hours to 450, 1110, 1170 cc. The ratio of the urine to the total amount of liquids ingested had increased to 1:2; that is, from one-sixth immediately after the operation to one-half.

On the seventh day the urea was 1.18 per cent, or 11.21 grams in the twenty-four hours. Albumin one-seventh per cent. Sediment was still considerable, but less than at first. Casts were fewer, chiefly hyaline, granular, fatty and epithelial; an occasional fibrinous cast, blood globule and cholesterin crystal; a few renal cells and leukocytes were also seen.

From that time the clinical picture changed. The temperature rose to 105° F., and from that time until the end ranged between 104° and 100° F. The pulse averaged from 130 to 140 beats per minute. The operation wounds which had apparently united by primary union were partially strained open superficially on the thirteenth day by the returning edema. The respiration averaged 35. Nausea and vomiting recurred on the thirteenth day.

The urine diminished in amount from 600 cc. to 230, 290, 300, 350, and to 338 cc. on the fifth day preceding the death. The amount of albumin ranged from one-seventh to one-third per cent. The urea varied from 4.6 grams in the twenty-four hours to 3.6 grams. The sediment increased toward the end and its fatty elements increased, and there were numerous free oil globules.

The remarkable results produced by decapsulation of a seriously diseased kidney have attracted marked attention. Surgically, attention is not so much directed today to the possibility of the operation, or its technique, for both have been conclusively demonstrated, neither is it a matter of doubt that patients suffering with advanced nephritic disease have apparently recovered after this operation, but it has not yet been accurately determined what varieties of renal disease are benefited by this treatment, or what are the limitations of the operation. The surgeon has not yet the knowledge which enables him to decide in what cases decapsulation can be performed with success and in what ones it is contraindicated, also in what cases it will relieve even if the patient is not cured, and in what cases the result will be a fatal one.

The case just reported, although unsuccessful, may be of service in contributing data to assist in acquiring this desired knowledge and for this purpose is reported. The patient was in an advanced stage of the disease presenting distinct uremic symptoms. The function of the kidney was seriously impaired. There could be only one termination, and that in a comparatively short time. It was then an operation done as a last resort. The fatal result was unexpected after it was found that the patient did not succumb to the operation. It was hoped, as two weeks had elapsed before the condition became alarming, and as for a greater part of that time the patient had done well, that eventually he would recover. It was expected that the operation would be the severest strain. That he endured it so well was an encouraging feature.

It has been estimated that a period of from three to four weeks is required to fairly establish the new circulatory renal conditions which are essential for the permanent recovery. Hence in a patient whose renal tissue is so disorganized that his excretory power would be insufficient for that period, this operation would be contraindicated. It has been stated that the diminution of the daily amount of urea to, or less, than one-third the normal amount indicates such deficient excretory power. In this case the rule

holds good, although in the beginning the course of the disease seemed to indicate that it would be an exception.

The effect of the anesthetic was interesting. It was, although continued for nearly one and a half hours, in no way, as far as could be seen, deleterious. The character of the urine improved immediately after the operation.

The effect of the operation on the edema was also striking. It was markedly diminished and continued so until three or four days before death, when it again began to reappear. This has been noted in other cases.

STREPTOMYCIN IN TUBERCULOUS MENINGITIS. (Settimana Medica, Florence, 39: 63, Feb. 15, 1951). During the last three years the authors have administered streptomycin to 55 patients with tuberculous meningitis. The drug was given subcutaneously and intraspinally, in doses varying with age, the response of the patient, and the stage of the disease when treatment began. As a rule, the dosage for adults was as follows: (1) subcutaneously: a daily dose of 2 gm. for 10 days and 1 gm. for three months; then alternating 10-day courses of streptomycin and paraaminosalicylic acid in daily doses of 1 gm. and 10 gm., respectively, from the fourth month up to the ninth month, followed by 20-day courses of streptomycin alternating with 10-day courses of paraaminosalicylic acid in daily doses of 0.5 gm. and 10 gm., respectively, for the last three months. The daily dose was given in two doses at intervals of 12 hours. (2) Intraspinally, a dose of 0.1 gm. was given daily for one month, every other day for three months, twice a week for three months, once a week for three months, and once a month for two months. Doses for infants and children were proportioned to those given adults. Ten patients who are still under treatment are improving; 16 patients were cured without sequelae and were able to return to work, and 29 patients died. The authors conclude that an early diagnosis and early treatment with streptomycin by both the subcutaneous and intraspinal routes are important. The drug, in the aforementioned doses, is well tolerated long enough for cure of tuberculous meningitis to be effected.—*Journal A.M.A.*

Archives of Pediatrics

A Monthly Journal Devoted to the

Diseases of Infants and Children

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VOLUME LXVIII

JANUARY TO DECEMBER

1951

E. B. TREAT & CO., INC., Publishers

45 East Seventeenth Street

NEW YORK

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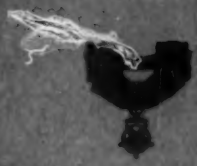

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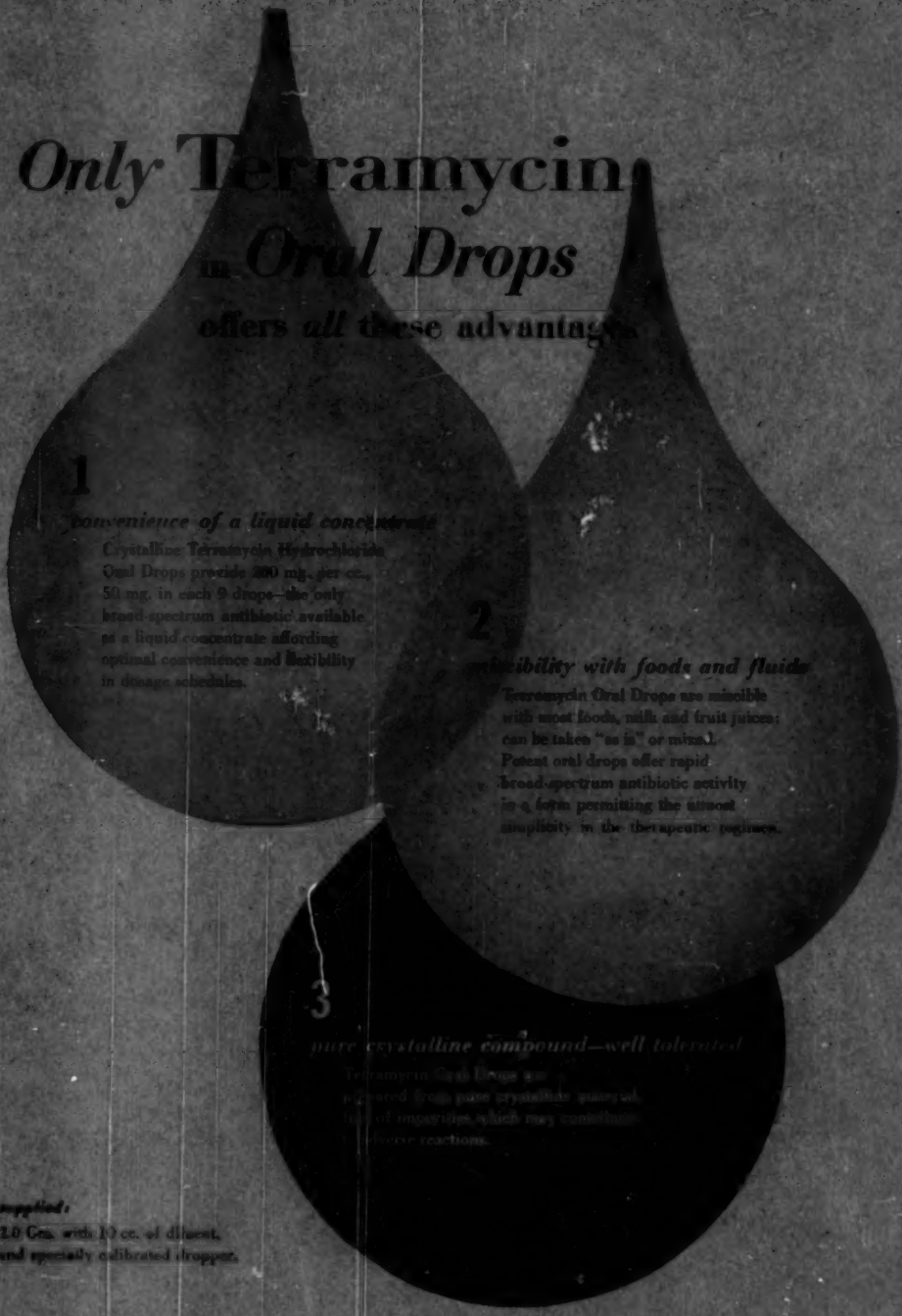

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